cancelled without prejudice. The subject matter of claims 41 and 44-50 is supported by the specification in that the specification discloses that DNA inserts up to 40 kb in size can be used in the claimed methods. See, for example, page 30, line 12 of the subject specification.

Claim 46 is objected to because it is allegedly incomplete and correction is required. In reply, applicant has corrected claim 46 by adding a period to the end of the claim. In view of these amendments, applicant respectfully requests the Examiner to reconsider and withdraw this ground of rejection.

Obviousness-Type Double Patenting Rejections

Claims 41-70 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of USPN 5,939,250. In addition, claims 41-70 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of USPN 5,958,672 in view of Arnold et al. (USPN 5,316,935).

Although applicant believes the above-referenced claims are clearly non-obvious over the cited art, applicant stands ready to submit terminal disclaimers to obviate the above-referenced obviousness-type double patenting rejections once the claims are

deemed to be in condition for allowance. Until that time, applicant requests the Examiner to hold this rejection in abeyance.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 41-70 stand rejected under 35 U.S.C. § 112, second paragraph for the following reasons.

(a) It is asserted that claim 41 omits essential steps as follows: (i) following step (a), isolating a DNA encoding a protein having a desired bioactivity; and (ii) need of a step to isolate the wild-type protein of interest to compare the mutant protein to it.

In reply, applicant traverses the rejection and maintains that claim 41 recites all essential steps. As to (i), there is no need to isolate a DNA encoding a protein having a desired bioactivity following step (a). Step (a) recites "creating a DNA library comprised of DNA molecules obtained directly from an environmental source." The introduction of mutations as recited in step (b) of claim 41 can be accomplished without first isolating a DNA encoding a desired bioactivity. For example, in one embodiment, the entire library can be subjected to mutagenesis in order to introduce the mutation(s) as recited in step (b) of claim 41. As to (ii), there is no need, necessarily, to isolate the wild-type protein of interest. The objective of the claim is to obtain a "desired bioactivity or biomolecule." This desired bioactivity or biomolecule is predefined. For

example, in one embodiment, the biomolecule is a known protein, having a known DNA sequence. There is no need, in this case, to include a step in the claim of isolating the wild-type protein of interest – such protein had already been isolated *a priori*. Thus, applicant requests the Examiner to reconsider and withdraw this ground of rejection.

(b) It is asserted that the phrase "a desired bioactivity or biomolecule" and "thru mutagenesis in directed evolution" render the claims indefinite. The Examiner states that the claims are drawn to a method of obtaining a mutant protein having desired and improved activity relative to that of the wild-type.

In reply, applicant traverses the rejection. Without conceding the correctness of the Examiner's position, applicant has amended claim 41 to delete the two conditional clauses at the end of the claim including the phrase "thru mutagenesis in directed evolution." Thus, applicant requests the Examiner to reconsider and withdraw this ground of rejection.

(c) It is asserted that claim 68 is indefinite in the limitation "enriching for a particular organism of interest." In reply, without conceding the correctness of the Examiner's position, applicant has amended claim 68 to recite "enriching for one or more DNA molecules of interest." Thus, applicant requests the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. § 102 (e)

Claims 41-70 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,824,485 to Thompson et al. The Examiner states that Thompson teaches a method for screening molecular diversity by mixing and cloning genetic material from plurality of species of organisms in a combinatorial gene library (abstract, § 6, col. 56-62). The Examiner also states that Thompson teaches that the genetic material can be obtained from any organism including those from environmental samples, plants and marine organisms to obtain antimicrobial, cancer or pharmaceutical compounds (see col. 12, line 35 – col. 16, line 35). The Examiner further asserts that Thompson teaches the isolation of nucleic acid sequence from soil or other mixed environmental samples (uncultured) (see § 5.3.6, col. 41 and §§ 5.4.1-5.4.14, cols. 42-50.

In reply, applicant respectfully traverses the rejection and maintains that Thompson does not teach or suggest the claimed invention which is directed to methods for obtaining a desired bioactivity or biomolecule, comprising: (a) creating a DNA library comprised of DNA molecules obtained directly from an environmental source; (b) introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and (c) screening to select a desired bioactivity or biomolecule containing a mutation.

Three types of libraries are discussed in Thompson et al.: (1) combinatorial natural pathway expression libraries; (2) combinatorial chimeric pathway expression libraries; and (3) biased combinatorial gene expression libraries. See claims 1-3 in col. 97 of Thompson. The libraries are prepared from genetic material that has been pre-selected for a specific property or from genetic material that is a derivation of what exists in a donor organism (see Thompson claims 1-3). Thompson states "the genetic material used to prepare the libraries can be obtained directly from an environmental sample" on lines 51-53 of col. 12.[1] However, this phrase is in the context of describing specifically *donor organisms* (see title of § 5.1.1 in col. 12) and not in the context of creating the library itself. Thompson discloses taking the genetic material "obtained directly from an environmental sample" and pre-selecting it prior to making the library. See, for example, col. 41, lines 25-50. Thompson also describes in col. 39, beginning at line 49, methods "for extracting, selecting and preparing high quality nucleic acids from culture of donor organisms." Thompson describes concentration of microbial samples, or amplification of DNA prior to creation of the library (see col. 17, lines 8-62). In contrast, the claimed invention requires "creating a DNA library comprised of DNA

[1] Applicants do not concede that the quotation from Thompson is supported in either of the priority documents (*i.e.*, U.S. Serial No. 427,244, filed April 25, 1995 and U.S. Serial No. 427,348, filed April 25, 1995). Accordingly, applicants do not concede that Thompson is entitled to the priority date of April 25, 1995 for this disclosure. Thompson (the '485 patent) is a continuation-in-part of the two aforementioned applications.

molecules obtained directly from an environmental source" (see step (a) of claim 41). For this reason, Thompson does not anticipate the claimed invention.

Withdrawal of the rejection of the pending claims under 35 U.S.C. § 102(e) is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 41-70 stand rejected under 35 U.S.C. § 103 as being unpatentable over Thompson et al. in view of Stemmer et al. (Proc. Natl. Acad. Sci. USA 1994, 91:10747-10751) and U.S. Patent No. 5,316,935 to Arnold et al. Thompson et al. is relied on for teaching, among other things, that recited in the 102(e) rejection above. Arnold et al. is asserted by the Examiner to disclose a method of obtaining mutants of subtilisin with desired characteristics which includes random mutagenesis of the gene encoding the enzyme by various methods. Stemmer et al. is asserted to teach a method of identifying proteins having a desired activity using nucleic acid shuffling. The Examiner asserts that Thompson "provides motivation for one of ordinary skill in the art to isolate a gene of interest from an environmental sample and generate a library of chimeric genes, and screen for desired product or enzymatic activity." It is also asserted that Stemmer "provide one of ordinary skill in the art with a motivation to develop a method of

identifying a protein with modified activity by generat[ing] a heterologous population of DNA from a gene encoding by mutagenesis."

In reply, applicant maintains that there is no motivation to combine the references and even if the references were combined, taken together, they do not teach or suggest the claimed invention. The asserted rejection lacks the specificity needed in finding a motivation to combine references. "[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed..." (underlining added, *In re Kotzab*, 217 F.3d 1365, 1375 (Fed. Cir. 2000)). The Examiner has pointed out that one of skill would be motivated by Thompson to do exactly what is taught by Thompson, *i.e.*, "isolate a gene of interest from an environmental sample and generate a library of chimeric genes, and screen for desired product..." (*see* page 6 of the October 5, 2001 Office Action). There is no indication of the motivation in Thompson to look to either Stemmer or Arnold for additional steps to the method disclosed by Thompson. Similarly, it is asserted in the October 5, 2001 Office Action that Stemmer provides motivation to one of ordinary skill in the art to do only what is actually disclosed by Stemmer. In particular, the Examiner states "also, Stemmer et al. provide one of ordinary skill in the art with a motivation to develop a method of identifying a protein with modified activity by generate [sic] a heterologous population of DNA from a gene

encoding [sic] by mutagenesis...." *See*, page 6, October 5, 2001 Office Action. The method of identifying a protein referred to here is simply the method which is described in Stemmer itself, not motivation to go outside of the reference and combine its teachings with something else. There is no indication in the October 5, 2001 Office Action of any motivation to one of ordinary skill in the art in one reference cited under 35 U.S.C. § 103 to go to one of the other references also cited, or to improve upon or alter the method in a single reference in any way. It seems that the Examiner then concludes, based apparently on nothing more than hindsight, that one of skill in the art would have combined Thompson and Stemmer. *See* October 5, 2001 Office Action, page 6, 4th ¶, lines 6-12. Thus, the applicant maintains that one of skill in the art would not have been motivated to combine Thompson with Stemmer or Arnold. "Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.* 159 F.3d 534, 546 (Fed. Cir. 1998).

Even if one were to combine the cited references (absent the required motivation), the combination would not make the claimed invention obvious to one of ordinary skill in the art. The remarks above which distinguish the claimed invention from the Thompson disclosure apply equally here. Furthermore, Stemmer merely discloses reassembly of genes from their random DNA fragments (see Abstract). There

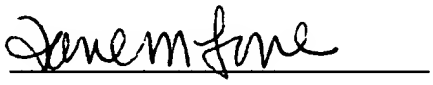
is no teaching or suggestion of step (a) of claim 41 directed to creating a DNA library comprised of DNA molecules obtained directly from an environmental source. There is no teaching or suggestion of introducing at least one mutation into a DNA molecule from said library, as required by step (b) of claim 41. Thus, the combination of Thompson and Stemmer does not teach or suggest the claimed invention. Similarly, the combination of Arnold et al. to the pairing of Thompson and Stemmer does not teach the claimed invention. The Arnold patent disclosure does not remedy the shortcomings of the combination of Thompson and Stemmer, in that Arnold does not teach or suggest introducing at least one mutation into a DNA molecule from a library comprised of DNA molecules obtained directly from an environmental source.

In conclusion, applicant maintains that the claimed invention is not rendered obvious by the combination of Thompson, Stemmer and Arnold. In addition, applicant maintains that there is no motivation to combine these three references and that, therefore, this rejection is improper under the law. In view of these remarks, applicant respectfully requests the Examiner to reconsider and withdraw these grounds of rejection and allow the pending claims to pass to issue.

Conclusi n

In view of the foregoing, it is believed that all objections and rejections of records have been overcome, and that the claims are in condition for allowance. Action towards that end is respectfully requested. The Examiner is invited to contact the undersigned attorney by telephone regarding any issues that may be handled in that fashion.

Respectfully submitted,



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APPENDIX 1

Annotated Version of Amendments to Specification

Please amend the fourth paragraph on page 6, line 11, to page 15, line 11 as follows:

The following outlines a general procedure for producing gene libraries from both culturable and non-culturable organisms.

Obtain Biomass

DNA Isolation

Shear DNA (25 gauge needle)

Blunt DNA (Mung Bean Nuclease)

Methylate (*Eco*R I Methylase)

Ligate to *Eco*R I linkers (GGAATTCC)

Cut back linkers (*Eco*R I Restriction Endonuclease)

Size Fractionate (Sucrose Gradient)

Ligate to lambda vector [Lambda ZAP II and gt11] (Lambda ZAP® II and gt11)

Package (*in vitro* lambda packaging extract)

Please amend the fourth paragraph on page 9, lines 10 and 11, to page 16 line, 11 as follows:

As representative examples of expression vectors which may be used there may be mentioned viral particles, baculovirus, phage, plasmids, phagemids, cosmids, phosmids, bacterial artificial chromosomes, viral DNA (*e.g.* vaccinia, adenovirus, foul pox virus, pseudorabies and derivatives of SV40), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (such as bacillus, aspergillus, yeast, *etc.*) Thus, for example, the DNA may be included in any one of a variety of expression vectors for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences. Large numbers of suitable vectors are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example; Bacterial: pQE70, pQE60, pQE-9 (Qiagen), psiX174, pBluescript® SK, pBluescript® KS(Stratagene); pTRC99a, pKK223-3, pDR540, pRIT2T (Pharmacia); Eukaryotic: pWLNEO, pXT1, pSG5 (Stratagene) pSVK3, pBPV, pMSG, pSVLSV40 (Pharmacia). Any other plasmid or vector may be used as long as they are replicable and viable in the host.

Please amend the second paragraph on page 22, line 3 and line 5 to page 16 and 17, line 4 and line 6 as follows:

Plates of the library prepared as described in Example 1 are used to multiply inoculate a single plate containing 200 μL of LB Amp/Meth, glycerol in each well. This step is preformed using High Density Replicating Tool (HDRT) of the Beckman [Biomek] BIOMEK® with a 1% bleach, water, isopropanol, air-dry sterilization cycle between each inoculation. The single plate is grown for 2h at 37°C and is then used to

inoculate two white 96-well [Dynatech] DYNATECH® microtiter daughter plates containing 250 μL of LB Amp/Meth, glycerol in each well. The original single plate is incubated at 37°C for 18h, then stored at –80°C. The two condensed daughter plates are incubated at 37°C also for 81 h. The condensed daughter plates are then heated at 70°C for 45 min. to kill the cells and inactivate the host *E. coli* enzymes. A stock solution of 5mg/mL morphourea phenylalanyl-7-amino-4-trifluoromethyl coumarin (MuPheAFC, the 'substrate') in DMSO is diluted to 600 μM with 50 mM pH 7.5 Hepes buffer containing 0.6 mg/mL of the detergent dodecyl maltoside.

Please amend the first paragraph on page 23, line 2 to page 17, line 2 as follows:

Fifty μL of the 600 μM MuPheAFC solution is added to each of the wells of the white condensed plates with one 100 μL mix cycle using the [Biomek] BIOMEK® to yield a final concentration of substrate of - 100 μM. The fluorescence values are recorded (excitation – 400 nm, emission – 505 nm) on a plate reading flurometer immediately after addition of the substrate (t=0). The plate is incubated at 70°C for 100 min, then allowed to cool to ambient temperature for 15 additional minutes. The fluorescence values are recorded again (t=100). The values at t=0 are subtracted from the values at t=100 to determine if an active clone is present.

Please amend the second paragraph on page 23, line 6 to page 17 and 18, line 6 as follows:

The data will indicate whether one of the clones in a particular well is hydrolyzing the substrate. In order to determine the individual clone which carries the activity, the source library plates are thawed and the individual clones are used to singly inoculate a new plate containing LB Amp/Meth, glycerol. As above, the plate is

incubated at 37°C to grow the cells, heated at 70°C to inactivate the host enzymes, and 50 µL of 600 µM MuPheAFC is added using [Biomek] BIOMEK®.

Please amend paragraph on page 26, line 7 and 16 to pages 18 and 19, line 6 and 14 as follows:

Reaction Cycle

95°C 15 seconds

58°C 30 seconds

72°C 90 Seconds

25 cycles (10 minute extension at 72°C-4°C incubation)

Run 5 microliters on a 1% agarose gel to check the reaction.

Purify on a quick [Qiaquick] QIAQUICK® column (Qiagen).

Resuspend in 50 microliters H_2O.

Restriction Digest

25 microliters purified PCR product

10 microliters NEB Buffer #2

3 microliters Kpn I (10U/microliter)

3 microliters EcoR1 (20U/microliter)

59 microliters H_2O

Cut for 2 hours at 37°C.

Purify on a [Qiaquick] QIAQUICK® column (Qiagen).

Elute with 35 microliters H_2O.

APPENDIX 2

Clean Version of Paragraphs of Specification as Amended

Please amend the fourth paragraph on page 6, line 11, to page 15, line 11 as follows:

The following outlines a general procedure for producing gene libraries from both culturable and non-culturable organisms.

Obtain Biomass

DNA Isolation

Shear DNA (25 gauge needle)

Blunt DNA (Mung Bean Nuclease)

Methylate (*Eco*R I Methylase)

Ligate to *Eco*R I linkers (GGAATTCC)

Cut back linkers (*Eco*R I Restriction Endonuclease)

Size Fractionate (Sucrose Gradient)

Ligate to lambda vector (Lambda ZAP® II and gt11)

Package (*in vitro* lambda packaging extract)

Please amend the fourth paragraph on page 9, lines 10 and 11, to page 16 line, 11 as follows:

As representative examples of expression vectors which may be used there may be mentioned viral particles, baculovirus, phage, plasmids, phagemids, cosmids, phosmids, bacterial artificial chromosomes, viral DNA (*e.g.* vaccinia, adenovirus, foul pox virus, pseudorabies and derivatives of SV40), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (such as bacillus, aspergillus, yeast, *etc.*) Thus, for example, the DNA may be included in any one of a variety of expression vectors for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences. Large numbers of suitable vectors are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example; Bacterial: pQE70, pQE60, pQE-9 (Qiagen), psiX174, pBluescript® SK, pBluescript® KS(Stratagene); pTRC99a, pKK223-3, pDR540, pRIT2T (Pharmacia); Eukaryotic: pWLNEO, pXT1, pSG5 (Stratagene) pSVK3, pBPV, pMSG, pSVLSV40 (Pharmacia). Any other plasmid or vector may be used as long as they are replicable and viable in the host.

Please amend the second paragraph on page 22, line 3 and line 5 to page 16, line 4 and line 6 as follows:

Plates of the library prepared as described in Example 1 are used to multiply inoculate a single plate containing 200 µL of LB Amp/Meth, glycerol in each well. This step is preformed using High Density Replicating Tool (HDRT) of the Beckman BIOMEK®_with a 1% bleach, water, isopropanol, air-dry sterilization cycle between each inoculation. The single plate is grown for 2h at 37°C and is then used to inoculate

two white 96-well DYNATECH® microtiter daughter plates containing 250 µL of LB Amp/Meth, glycerol in each well. The original single plate is incubated at 37°C for 18h, then stored at –80°C. The two condensed daughter plates are incubated at 37°C also for 81 h. The condensed daughter plates are then heated at 70°C for 45 min. to kill the cells and inactivate the host *E. coli* enzymes. A stock solution of 5mg/mL morphourea phenylalanyl-7-amino-4-trifluoromethyl coumarin (MuPheAFC, the 'substrate') in DMSO is diluted to 600 µM with 50 mM pH 7.5 Hepes buffer containing 0.6 mg/mL of the detergent dodecyl maltoside.

Please amend the first paragraph on page 23, line 2 to page 17, line 2 as follows:

Fifty µL of the 600 µM MuPheAFC solution is added to each of the wells of the white condensed plates with one 100 µL mix cycle using the BIOMEK® to yield a final concentration of substrate of - 100 µM. The fluorescence values are recorded (excitation – 400 nm, emission – 505 nm) on a plate reading flurometer immediately after addition of the substrate (t=0). The plate is incubated at 70°C for 100 min, then allowed to cool to ambient temperature for 15 additional minutes. The fluorescence values are recorded again (t=100). The values at t=0 are subtracted from the values at t=100 to determine if an active clone is present.

Please amend the second paragraph on page 23, line 6 to page 17, line 6 as follows:

The data will indicate whether one of the clones in a particular well is hydrolyzing the substrate. In order to determine the individual clone which carries the activity, the source library plates are thawed and the individual clones are used to singly inoculate a new plate containing LB Amp/Meth, glycerol. As above, the plate is

E11

incubated at 37°C to grow the cells, heated at 70°C to inactivate the host enzymes, and 50 µL of 600 µM MuPheAFC is added using BIOMEK®.

Please amend paragraph on page 26, line 7 and 16 to pages 17 and 18, line 6 and 14 as follows:

Reaction Cycle

95°C 15 seconds

58°C 30 seconds

E12

72°C 90 Seconds

25 cycles (10 minute extension at 72°C-4°C incubation)

Run 5 microliters on a 1% agarose gel to check the reaction.

Purify on a quick QIAQUICK® column (Qiagen).

Resuspend in 50 microliters H_2O.

Restriction Digest

25 microliters purified PCR product

10 microliters NEB Buffer #2

3 microliters Kpn I (10U/microliter)

3 microliters EcoR1 (20U/microliter)

59 microliters H_2O

Cut for 2 hours at 37°C.

E13

Purify on a QIAQUICK® column (Qiagen).

Elute with 35 microliters H_2O.

APPENDIX 3

Annotated Version of Claim Amendments

41. (Amended) A method for obtaining a desired bioactivity or biomolecule, comprising:

(a) creating a DNA library comprised of DNA molecules obtained directly from an environmental source;

(b) introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and

(c) screening to select a desired bioactivity or biomolecule containing a mutation. [whereby, if desired, biomolecules can be accessed from uncultivated organisms, and if desired, improved thru mutagenesis in directed evolution.]

46. (Amended) The method of claim 43, wherein the genomic DNA is at least 10 kb in size.

64. (Amended) The method of claim 63, wherein the vector includes chromosomal, nonchromosomal or [syntheitic] synthetic DNA.

68. (Amended) The method of claim 41, further comprising:

[c)] d) enriching for one or more DNA molecules [a particular organism or organisms] of interest.

Please add new claims 71-72 as follows:

71. (New) The method of claim 41, wherein the bioactivity is an enzymatic activity.

72. (New) The method of claim 71, wherein the enzymatic activity is hydrolase activity, polyketide synthase activity, alkaline phosphatase activity, or beta-glycosidase activity.

APPENDIX 4

Clean Version of All Pending Claims With Amendments

41. (Amended) A method for obtaining a desired bioactivity or biomolecule, comprising:

a) creating a DNA library comprised of DNA molecules obtained directly from an environmental source;

b) introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and

c) screening to select a desired bioactivity or biomolecule containing a mutation.

42. The method of claim 41, further comprising the step of:

d) expressing the mutagenized molecule of step (b) to create a bioactivity or biomolecule containing a mutation.

43. The method of claim 41, wherein, for step a), the DNA is genomic DNA.

44. The method of claim 43, wherein the genomic DNA is at least 1 kb in size.

45. The method of claim 43, wherein the genomic DNA is at least 5 kb in size.

46. (Amended) The method of claim 43, wherein the genomic DNA is at least 10 kb in size.

47. The method of claim 43, wherein the genomic DNA is at least 15 kb in size.

48. The method of claim 43, wherein the genomic DNA is at least 20 kb in size.

49. The method of claim 43, wherein the genomic DNA is at least 30 kb in size.

50. The method of claim 43, wherein the genomic DNA is at least 35 kb in size.

56. The method of claim 41, wherein the DNA comprises at least one gene cluster.

57. The method of claim 41, wherein the DNA encodes a gene cluster involved in production of polyketide synthases.

58. The method of claim 41, wherein the DNA encodes a gene cluster involved in production of polyketides.

59. The method of claim 58, wherein the polyketides are selected from the group consisting of antibiotics, anti-cancer agents, and immunosuppressants.

60. The method of claim 41, wherein the DNA encodes a molecule useful in a veterinary product.

61 The method of claim 41, wherein the DNA encodes at least one operon.

62. The method of claim 41, wherein, for step a), the library is made using a vector.

63. The method of claim 62, wherein the vector is selected from the group consisting of viral particles, baculovirus, phage, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, and viral DNA

64. (Amended) The method of claim 63, wherein the vector includes chromosomal, nonchromosomal or synthetic DNA.

64

65. The method of claim 63, wherein the vector contains suitable regulatory sequence for effecting expression of at least a portion of the DNA.

66. The method of claim 41, wherein, for step a), where the environmental sample is obtained from a locality selected from the group consisting of arctic, antarctic, volcanic and tropical locations.

67. The method of claim 64, wherein in the environmental sample is soil, water, permafrost, or plant.

68. (Amended) The method of claim 41, further comprising:

65

d) enriching for one or more particular DNA molecules of interest.

69. The method of claim 41, wherein the DNA is derived from a plurality of donor organisms.

70. The method of claim 65, wherein step (c) is comprised of hybridization screening.

71. (New) The method of claim 41, wherein the bioactivity is an enzymatic activity.

72. (New) The method of claim 71, wherein the enzymatic activity is hydrolase activity, polyketide synthase activity, alkaline phosphatase activity, or beta-glycosidase activity.